



Medegen, Inc.'s Comments on the Draft Guidelines for the Prevention of Intravascular Catheter-Related Infections

Medegen, Inc., ("Medegen"), a manufacturer of positive pressure needleless connector devices, submits the following comments to the draft *Guidelines for the Prevention of Intravascular Catheter-Related Infections* ("Draft Guidelines").ⁱ

Introduction

Specifically, Medegen comments on the section of the Draft Guidelines entitled "Needleless Intravascular Catheter Systems" ("NICS Section").ⁱⁱ Primarily, we are concerned about the following recommendation: "6. When needleless systems are used, the split septum valve is preferred over the mechanical valve due to increased risk of infection [336-339]. Category II."ⁱⁱⁱ These comments refer to this as the "Split Septum Recommendation" or the "Recommendation."

Specific Comments

1. The Split Septum Recommendation is vague because it does not define "split septum valve" or "mechanical valve."

Only one specific "split septum" device manufactured by one specific manufacturer was covered by the four studies upon which the Recommendation relies (the "SSR Studies").^{iv} Currently, four other domestically marketed designs are called "split septum" by their manufacturers. Also, various definitions of "split septum" exist in the marketplace. The specific split septum device covered by the SSR Studies is categorized as "External Cannula Activated Split Septum"; yet, this is not specified in the Recommendation. As worded, the Recommendation could be interpreted as recommending all devices that are called "split septum" but that vary in device design significantly. Those other "split septum" designs differ substantially from each other and from the "split septum" design studied by the SSR Studies. Also, those other designs incorporate mechanical components other than a split septum. To provide workable guidance, the Recommendation should clearly define the terms "the split septum valve" and "the mechanical valve." Additionally, reliable bases for the definitions and the distinctions between them must be provided.^v

2. The Split Septum Recommendation is not adequately supported by the SSR Studies. Support is inadequate for the following reasons.

2.1. The SSR Studies were *post hoc*, uncontrolled, even unblinded. They were *post hoc* because their research questions were formulated after their authors noticed a sharp increase in the rate of bloodstream infection ("BSI") in patient populations during specific time periods and conducted retrospective studies in the same populations over the same time periods. They were unblinded, although the investigators that classified

cases of BSI as associated with catheter use could have been blinded to the type of device used.⁶ Both of these limitations rendered the Studies highly susceptible to bias.⁷

Given these limitations, the SSR Studies did not establish that any device caused any increase in BSI rates.⁸ Additionally, the Studies spoke in terms of a “temporal association” but did not establish an epidemiological association between any device and an increase in BSI rates.⁹

2.2. Setting aside those limitations, the results of the SSR Studies do not support the Recommendation. This can be seen by examining device-specific BSI rates reported in the Studies.

Maragakis 2006 studied two mechanical valve designs, one negative and one positive pressure (a split septum device was not studied). In that institution, the BSI rates that occurred during use of the negative pressure mechanical valve device in all ICUs and the Children’s Center (overall) were lower than – and the rates that occurred during use of the positive pressure device were comparable to – the rates that occurred during use of the split septum device reported in *Field 2007*.

Also in the *Maragakis* institution, the BSI rates that occurred during use of the introduced positive pressure mechanical valve device in all ICUs and the Children’s Center were lower than the baseline BSI rates that occurred during use of the split septum device in the *Rupp 2007* institution’s Critical Care and Transplantation, Inpatient Nursing and Cooperative Care Transplantation units. In fact, both Studies studied the same positive pressure mechanical valve design from the same manufacturer. The BSI rates that occurred during use of that device design were much lower in the *Maragakis* institution than in the *Rupp* institution.

Finally, although *Field 2007* did not report BSI rates for the specific mechanical valve devices, the *Field* institution rejected use of the same negative pressure mechanical valve device that the *Maragakis* institution approved.

Even though these cross-study comparisons are not controlled and are from different patient groups, they indicate that:

- The mechanical valve devices could be used to mitigate BSI rates as effectively as the split septum device;
- In the institutions covered by the Studies, causes of increased BSI rates other than device design were likely. This is especially important given that the within-study comparisons are not controlled and do not rule out such possible alternative causes.

2.3. Three SSR Studies (*Maragakis 2006*, *Rupp 2007* and *Salgado 2007*) covered programs in which the mechanical valve devices were not used in accordance with the manufacturers’ instructions but were used in manners that likely increased BSI rates.

The manufacturer of the mechanical valve devices used by the institutions covered by

those Studies instructed users to replace the devices every 72 hours or 100 activations, whichever occurred first; for infusions of blood, blood products or lipid emulsions, the device was to be replaced every 24 hours. In *Maragakis 2006* and *Salgado 2007*, the institutions replaced the devices every 96 hours. In *Rupp 2007*, the institution replaced the device every 7 days. The fourth Study, *Field 2007*, did not specify the manner of device use. To be a valid basis for these Draft Guidelines, data should be generated consistent with use of the devices in accordance with manufacturers' instructions. The SSR Studies did not generate such data.

2.4. Even if the SSR Studies had established an association between the devices studied and increased infection rates, there would exist no reliable basis for extrapolating from the experience of that device to devices of other designs.

Maragakis 2006 and *Field 2007* did not provide data by which to compare BSI rates between any split septum device and any specific mechanical valve device. *Maragakis 2006* did not compare any mechanical valve device to any split septum device. *Field 2007* did not report BSI rates specific to either mechanical valve device it covered. Since the infection rates for individual mechanical valve devices were not reported, it is possible that one of the devices had comparable or lower infection rates than the split septum device. The direct comparisons between mechanical valve devices and the split septum device were made by *Rupp 2007* and *Salgado 2007*.

Rupp 2007 compared one positive pressure mechanical valve device to one split septum device. *Salgado 2007* compared one negative pressure mechanical valve device to the same split septum device covered by *Rupp 2007*.

Devices compared in *Rupp 2007* and *Salgado 2007*

Study	Split Septum Device	Negative Pressure Device	Positive Pressure Device
<i>Rupp 2007</i>	Interlink	None	SmartSite Plus
<i>Salgado 2007</i>	Interlink	SmartSite	None

The mechanical valve devices in *Rupp* and *Salgado* were from the same manufacturer and had similar properties pertaining to surface cleaning, flushing and fluid trapping. Together, those three devices constitute only about 30 percent of the market. The remaining 70 percent of the market is comprised of at least fourteen (14) other mechanical device designs.

Marketed Devices not Studied by or not Directly Compared With the Split Septum Device in the SSR Studies

1	MaxPlus / FloLink	8	Invision
2	MaxPlus Clear	9	Clave
3	MaxGuard	10	MicroClave
4	Clearlink	11	CLC-2000

5	V-Link	12	UltraSite
6	Posiflow	13	RobertSite
7	Qsyte	14	Flo-Star

As noted by the *Draft Guidelines*: “The physical and mechanical properties of second-generation connectors vary widely from device to device.”¹⁰ Thus, there is no basis to extrapolate from one split septum device and two mechanical valve devices that possess identical access surfaces and nearly identical internal fluid paths to the remainder of marketed products. Such extrapolation is inappropriate, especially because the SSR Studies are based on the use of mechanical valve devices in programs that were not designed to incorporate them: all four SSR Studies reported that they did not change their device use protocols when the mechanical valve devices replaced the split septum device.¹¹

Proposals

Based on these considerations, we have two proposals. First, we propose that the Split Septum Recommendation be stricken and replaced with the following language:

Before being used, needleless connection systems should be evaluated for design features that aid in disinfection practices, especially, surface cleaning, thorough flushing and lack of fluid trapping.

Second, we propose that the discussion of device properties in the NICS Section¹² be restated as criteria by which devices should be evaluated for use. Specifically, the following criteria for assessing needleless connection devices should be stated in the NICS Section:

- Can access surfaces be disinfected through reasonable procedures? For example, does the device leave a gap between the valve and the hub that cannot be adequately sterilized?
- Do gaps, depressions or other areas exist that cannot be adequately disinfected? For example, are there physical characteristics of the plastic housing diaphragm interface that would make adequate disinfection difficult?
- Does the fluid path contain reservoirs in which fluid could be trapped and which could foster the growth of microbial contaminants? For example, are there areas of potential fluid dead space or internal corrugations that could harbor organisms?
- Can the device be thoroughly flushed?
- Is the device housing clear so that the fluid flow pathway can be visualized and thorough flushing verified?
- Can the use of an antiseptic barrier cap promote better disinfection with the device?

¹ Department of Health and Human Services, Centers for Disease Control and Prevention (CDC), *Draft Guidelines for the Prevention of Intravascular Catheter-Related Infections*, 74 Fed. Reg. 56843 (Nov. 3, 2009) (hereinafter *Draft Guidelines*).

² *Draft Guidelines* at 47:1064 – 50:1131.

³ *Draft Guidelines* at 48:1078-1079.

⁴ The four studies are cited in the *Draft Guidelines* as references 336-339: Rupp M.E., et al., *Outbreak of bloodstream infection temporally associated with the use of an intravascular needleless valve*, Clin Infect Dis 44:1408-14 (2007) (hereinafter *Rupp 2007*); Salgado C.D., et al, *Increased rate of catheter-related bloodstream infection associated with use of a needleless mechanical valve device at a long-term acute care hospital*, Infect Control Hosp Epidemiol 28:684-8 (2007) (hereinafter *Salgado 2007*); Maragakis L.L. et al., *Increased catheter-related bloodstream infection rates after the introduction of a new mechanical valve intravenous access port*, Infect Control Hosp Epidemiol 27:67-70 (2006) (hereinafter *Maragakis 2006*); Field K., et al., *Incidence of catheter-related bloodstream infection among patients with a needleless, mechanical valve-based intravenous connector in an Australian hematology-oncology unit*, Infect Control Hosp Epidemiol 28:610-3 (2007) (hereinafter *Field 2007*).

⁵ The remainder of these comments assume that the SSR Recommendation uses the term “split septum” to mean the design of the device referred to by that name in the SSR Studies. This assumption is based on the fact that only one device called “split septum” was covered by those Studies.

⁶ Lack of blinding is important, given the following statement in the *Draft Guidelines*:

The rate of all catheter-related infections, including local infections and systemic infections, is difficult to determine. Potentially infectious episodes must be evaluated clinically and microbiologically and documented in the record; the data must be reviewed by well informed and fairly adjudicated personnel as to whether an episode is due to infection or contamination and if infection is present, whether it is related to the CVC or to a secondary source.

Draft Guidelines at 5:119-124.

⁷ The Studies may have been affected by sources of bias such as the following: inaccurate dates of device introduction, “lapses in intravascular catheter care” (*Rupp 2007* at 1412), lack of effectiveness of *status quo ante* catheter care procedures for newly introduced devices, “variation in CR-BSI rates over time” (*Maragakis 2006* at 69), and differences patient in populations over time. Further, the Studies’ results are confusing, because the Studies were conducted in different patient groups that faced different risks of infection and in which different catheter designs were used, but for which the design-specific risks of infection were not reported.

⁸ See e.g., *Rupp 2007* at 1413 (“Although causation can not [sic] be concluded from these data . . .”).

⁹ See e.g., *Maragakis 2006* at 68 (“In the present study, we report a **temporal association** . . .” (emphasis added)); *Id.* at 69 (“Further study is needed to determine whether access ports with MVs and/or the relatively new positive-pressure design are associated with microbiological contamination and CR-BSIs.”); *Salgado 2007* at 687 (“We agree with Maragakis et al. that healthcare facilities should be aware that infection control-related problems **could be associated** with the use of these needleless IV infusion systems . . .” (citations omitted, emphasis added)); *Field 2007* at 613 (“Our findings, consistent with those from emerging reports elsewhere, suggest that colonization of MV connectors **may be associated** with increased rates of catheter-associated BSI.” (citations omitted, emphasis added)).

¹⁰ *Draft Guidelines* at 50:1119-1120.

¹¹ *Maragakis 2006* at 67 (“There were no changes to the vascular access device policy during the period of this study.”); *Field 2007* at 611 (“Apart from changes in connectors, there were no alterations in staffing levels, line types or supplier, intravenous fluids, catheter insertion policy and method, barrier precautions, nursing education or educational campaigns, blood culture policy and procedures, or dressing and other equipment used.”); *Rupp 2007* at 1409 (“No changes were instituted in catheter insertion or care protocol during the observation periods.”); *Salgado 2007* at 685 (“During the study period, there were no changes in the hospital policy regarding the care of central venous catheters.”).

¹² *Draft Guidelines* at 50:1119-1131.